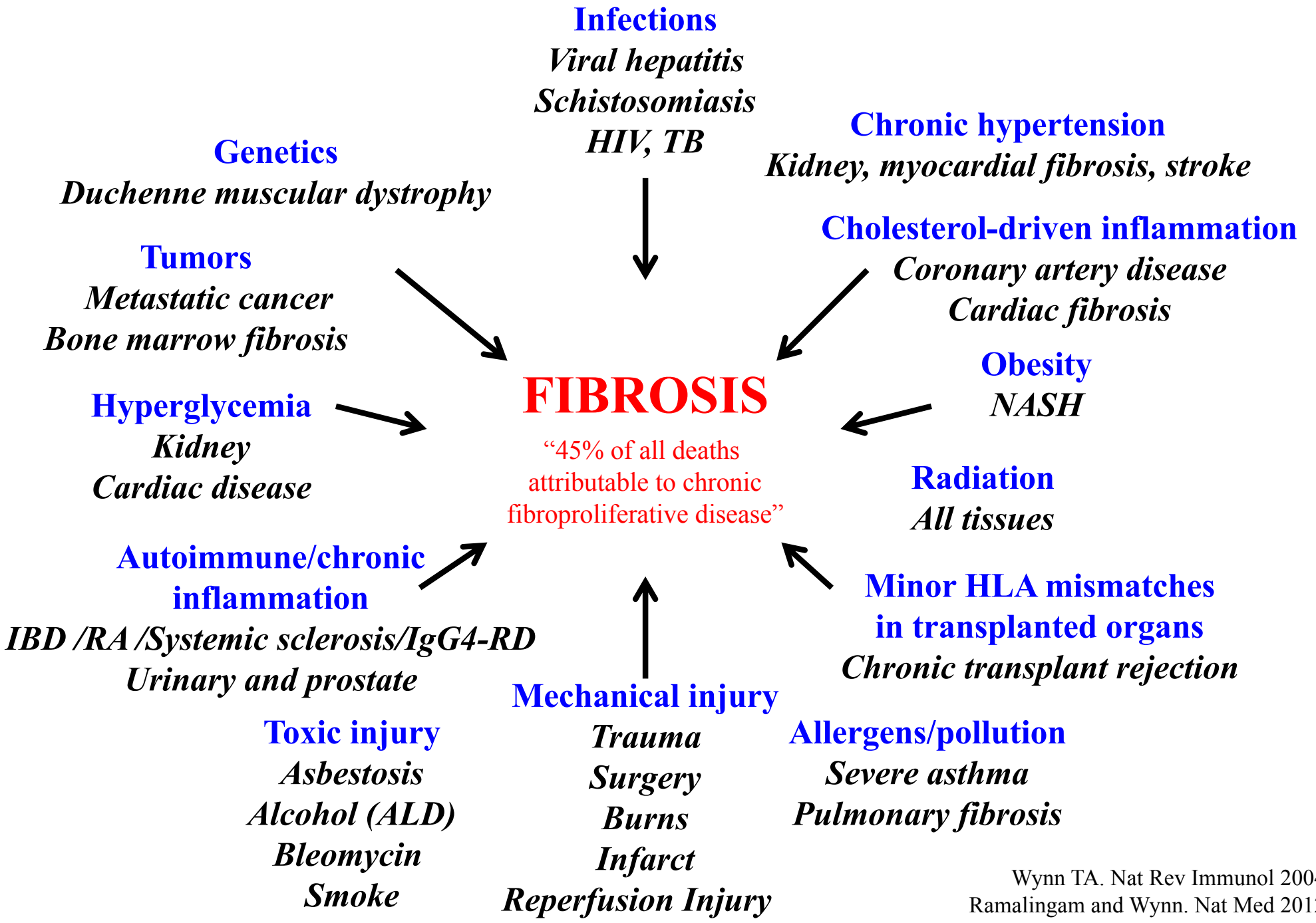
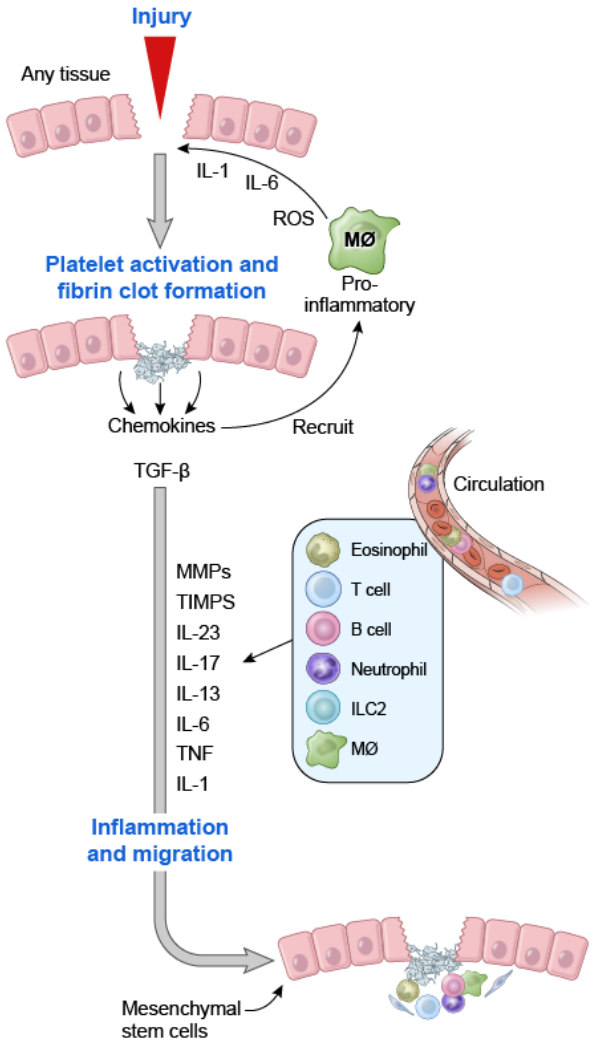


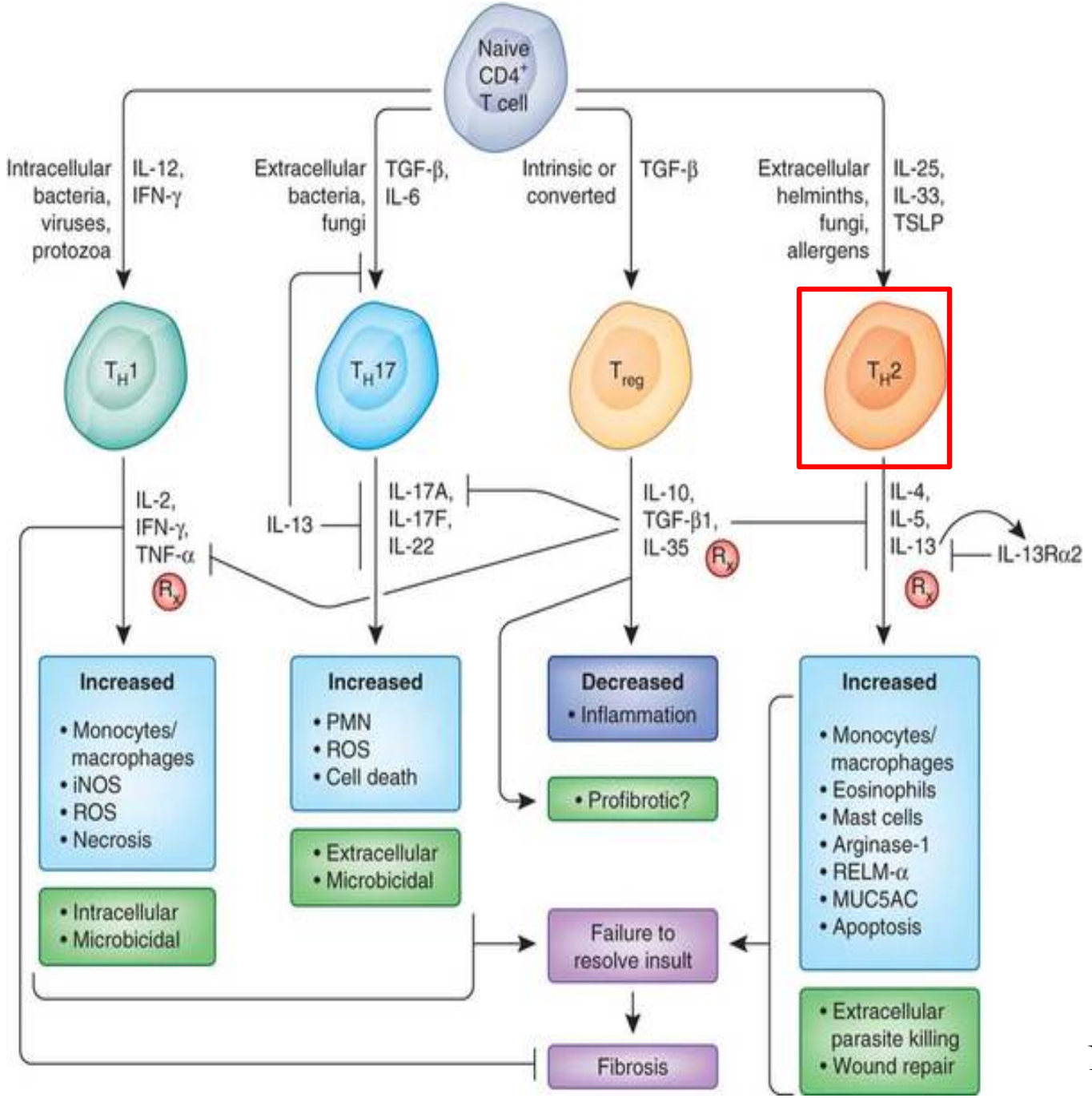
Wynn TA. Nat Rev Immunol 2004
Ramalingam and Wynn. Nat Med 2012

Regulation of tissue repair and fibrosis by inflammatory mediators

Cancer



Key role for TGF-β1 and type 2 immunity in fibrosis

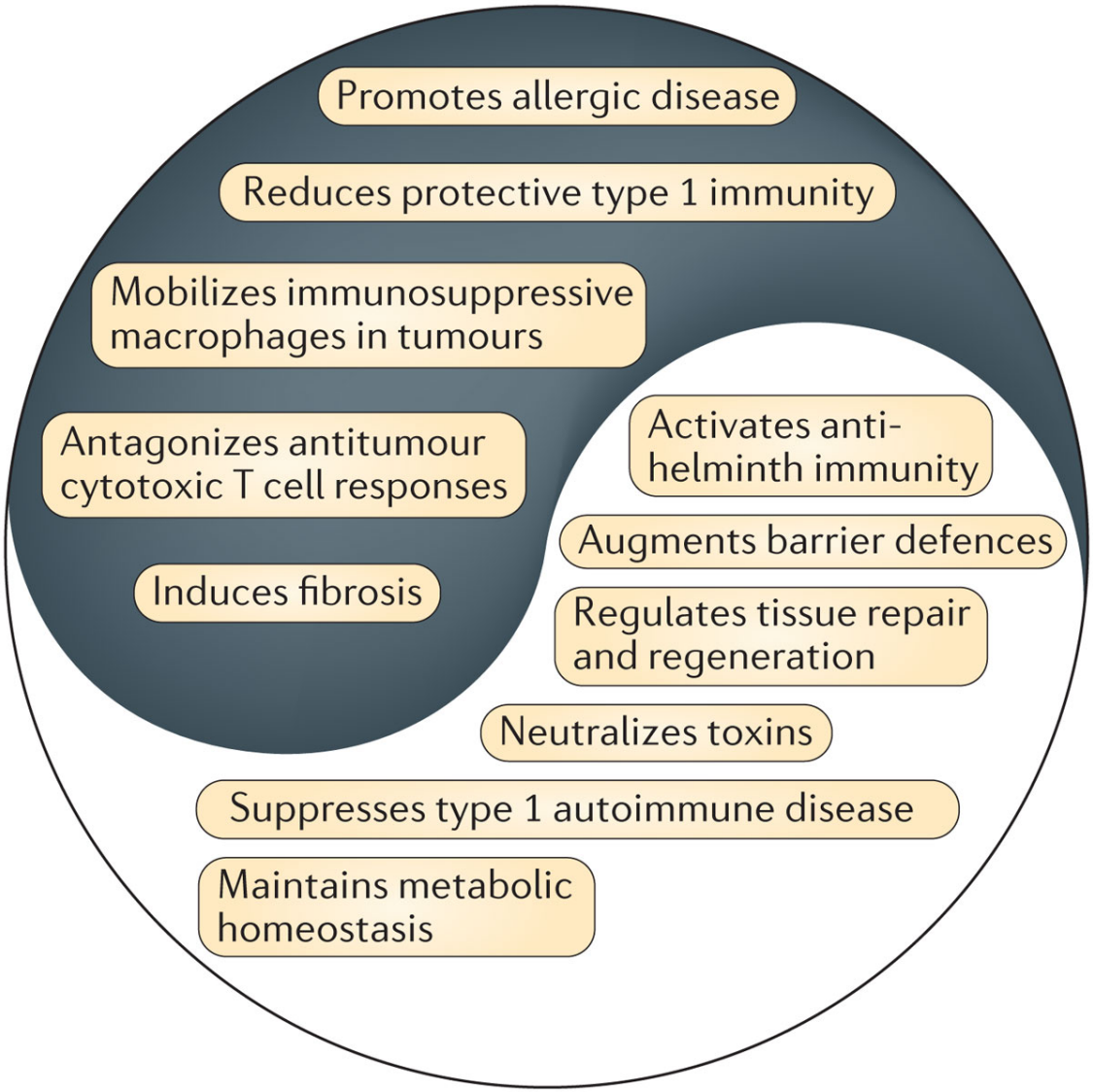


Nat Med 2012

Type 2 immunity in repair and fibrosis

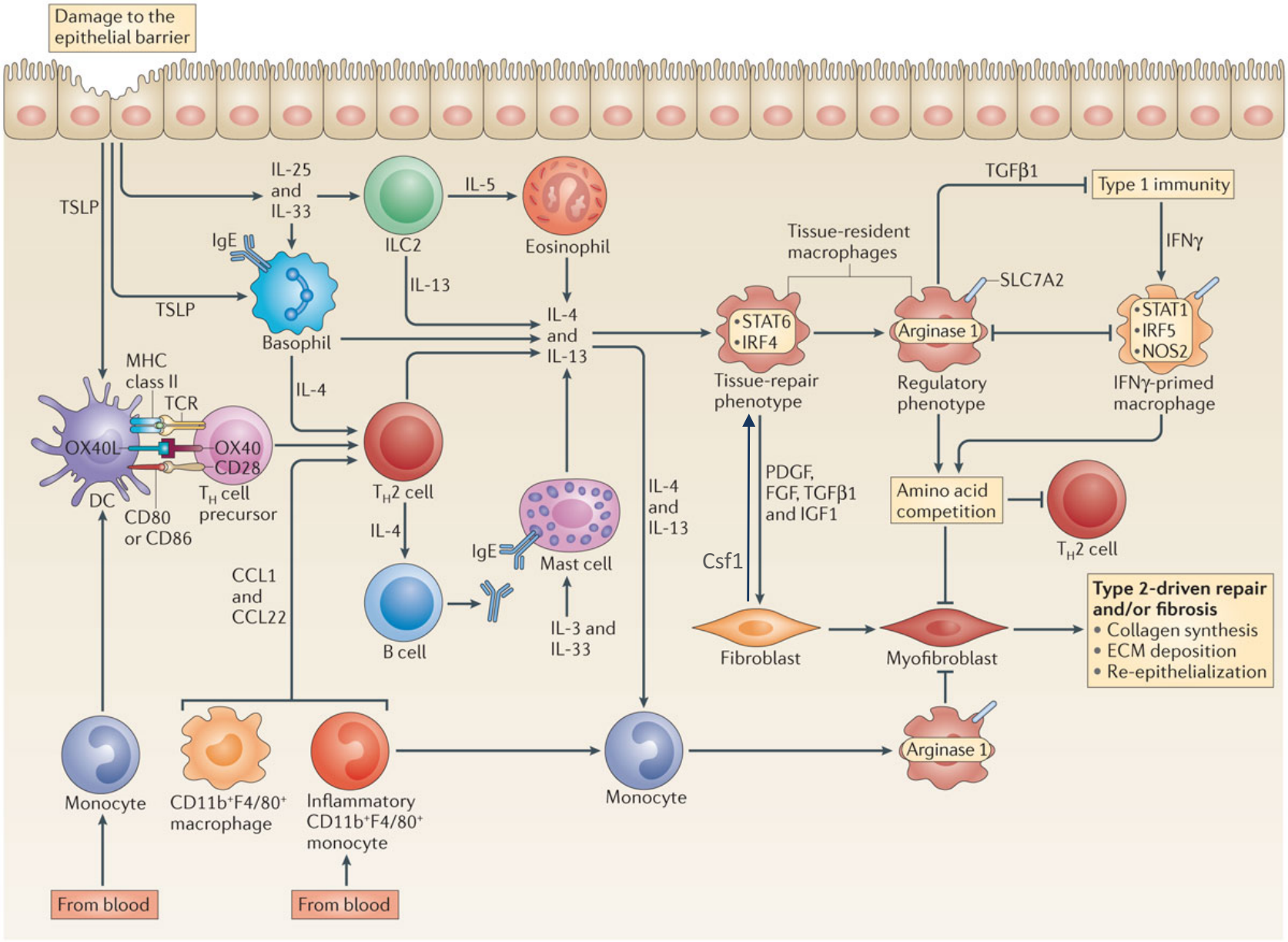
IL-4
IL-5
IL-9
IL-13

$CD4^+$ Th2
Eosinophils
M2 macs
Basophils
Mast cells
ILC2



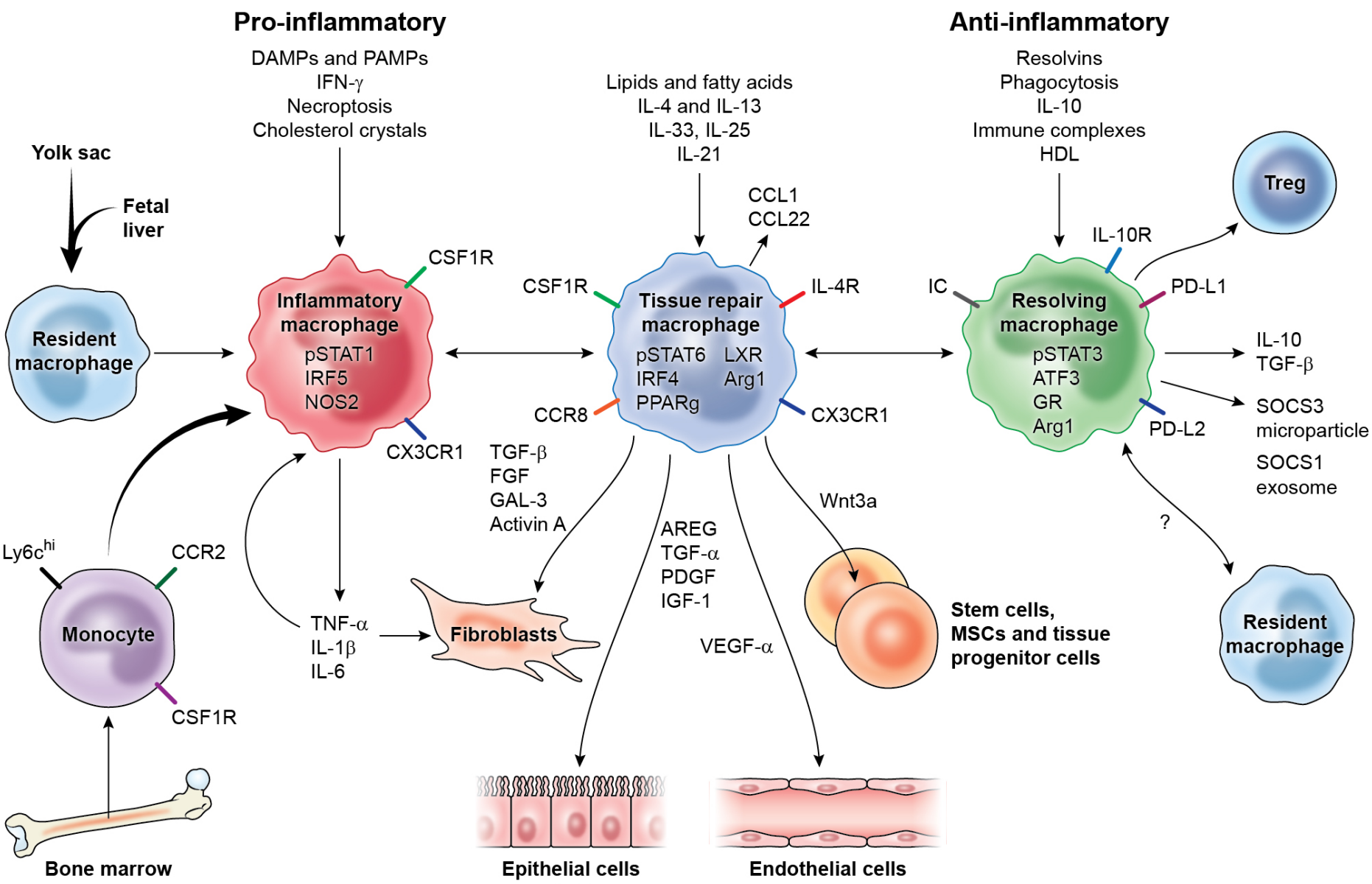
Nature Reviews | Immunology

Type 2 response in repair and fibrosis: Prevailing Paradigm

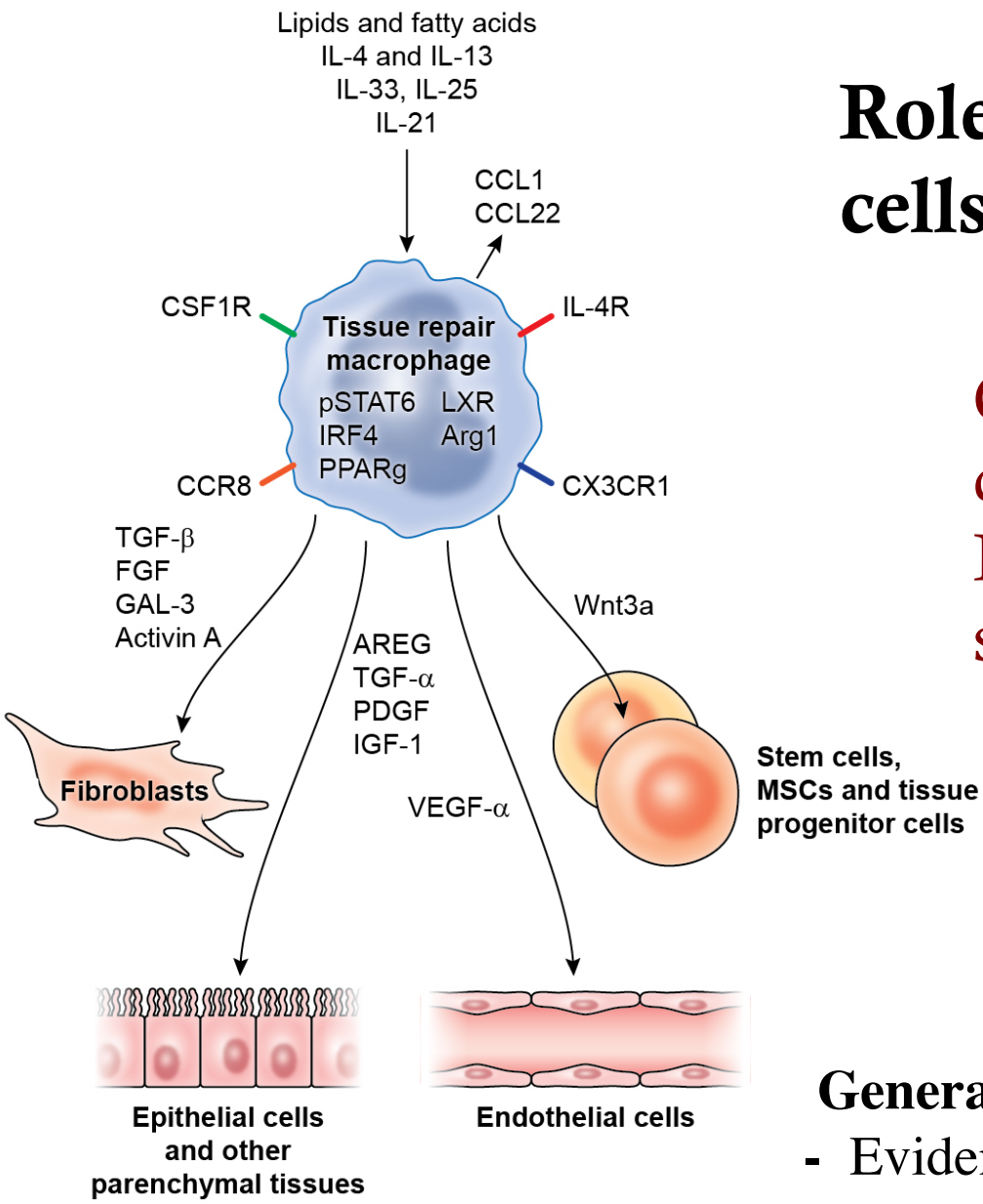


Nature Reviews | Immunology

Tissue repair macrophages: critical to tissue regeneration and fibrosis?



Wynn, TA, Vannella KM. Macrophages in Tissue Repair, Regeneration, and Fibrosis. Immunity. 2016 Mar



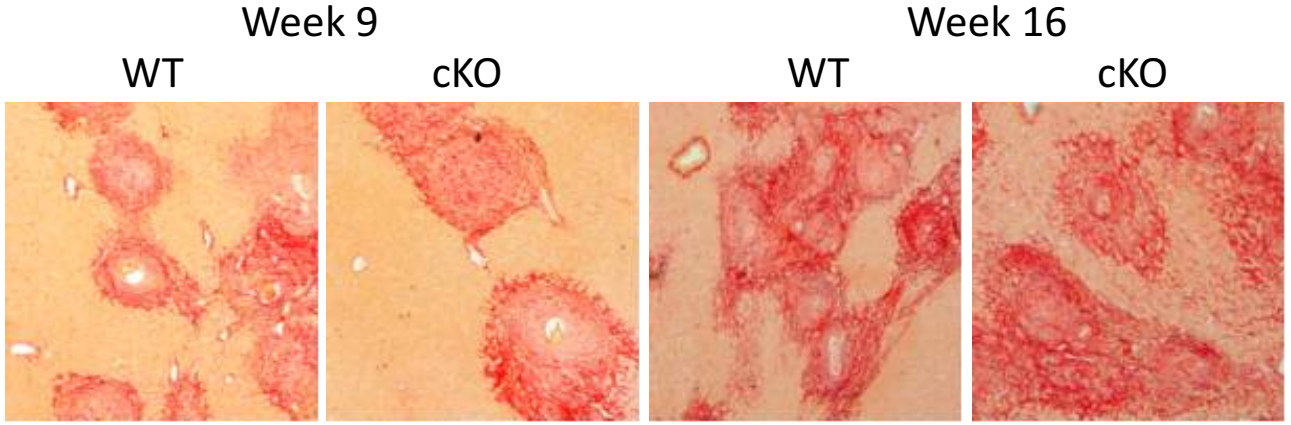
Role of IL-4/13 responsive cells in repair and fibrosis?

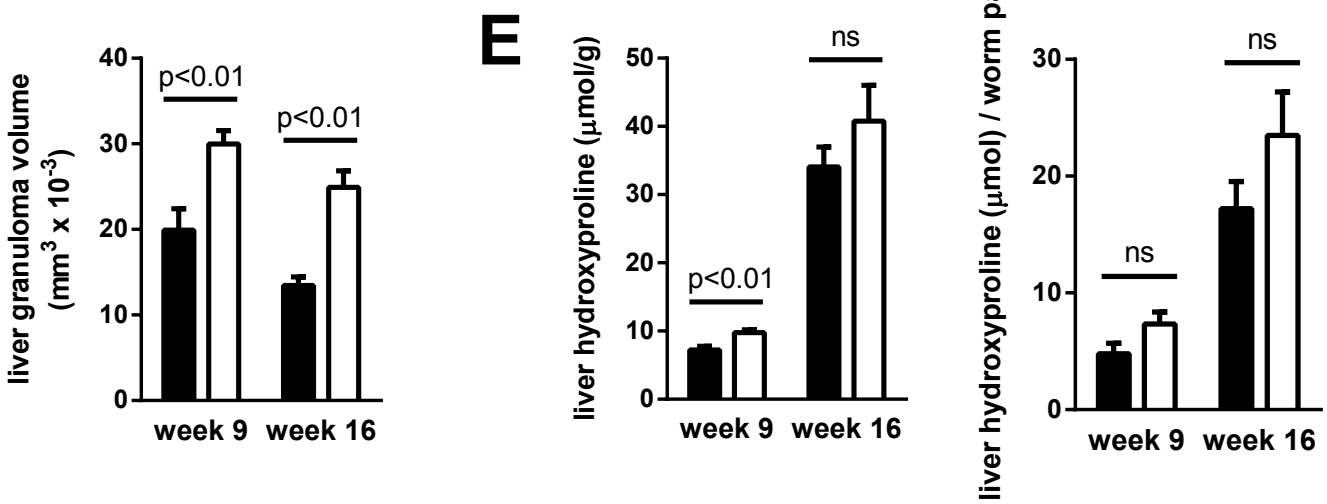
Generation of cell specific deletions of IL-4Rα chain using IL-4Ra$^{flox/flox}$ mice crossed with specific cre expressing strains

Generation of LysM-Cre IL-4Rα $^{flox/flox}$ mice

- Evidence IL-4Rα deletion in resident tissue macrophages but not inflammatory monocytes

Resident *Lyz2*^{hi}IL-4Rα^{+}CD11b^{+}F4/80^{+} macrophages suppress chronic inflammation in schistosomiasis

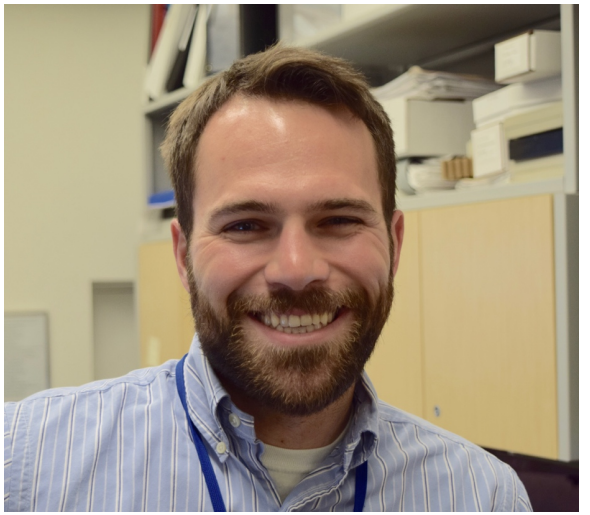




Evidence that M2 cells are not critical for repair or fibrosis and in fact play a suppressive role

What about other IL-13 responsive cells?

~~Resident tissue M2 macs~~ M2-like monocytes?
Hepatocytes
Biliary cells – cholangiocytes (epithelium)
Hepatic progenitor cells
Fibroblasts



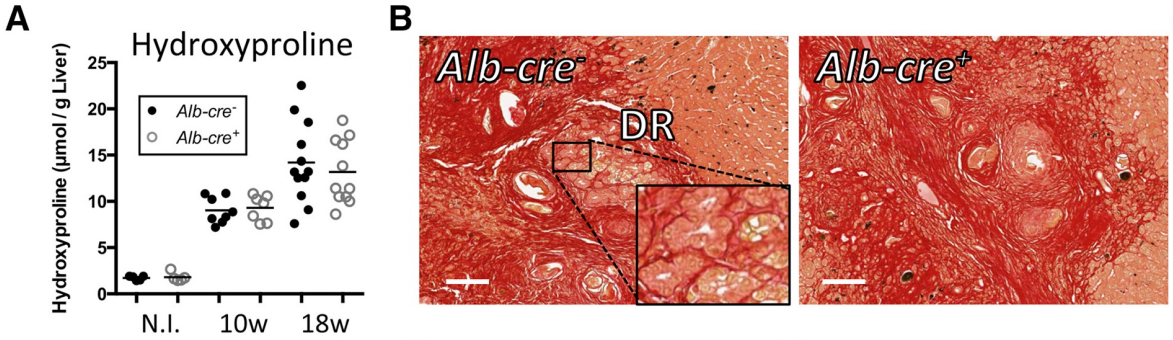
Generation of Albumin-Cre IL-4Rα $^{flox/flox}$ mice

- Deficiency in IL-4/IL-13 signaling in hepatocytes and biliary compartment

Hepatocytes
Biliary cells – cholangiocytes

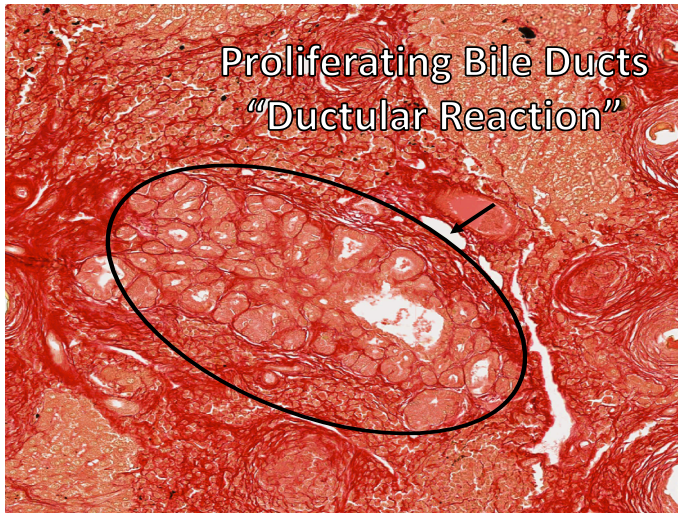
Liver regeneration (bile duct proliferation) is uncoupled from fibrosis in IL-4Rα$^{flox/flox}$;Alb cre+ mice

(IL-4R+ hepatocytes not critical for fibrosis)

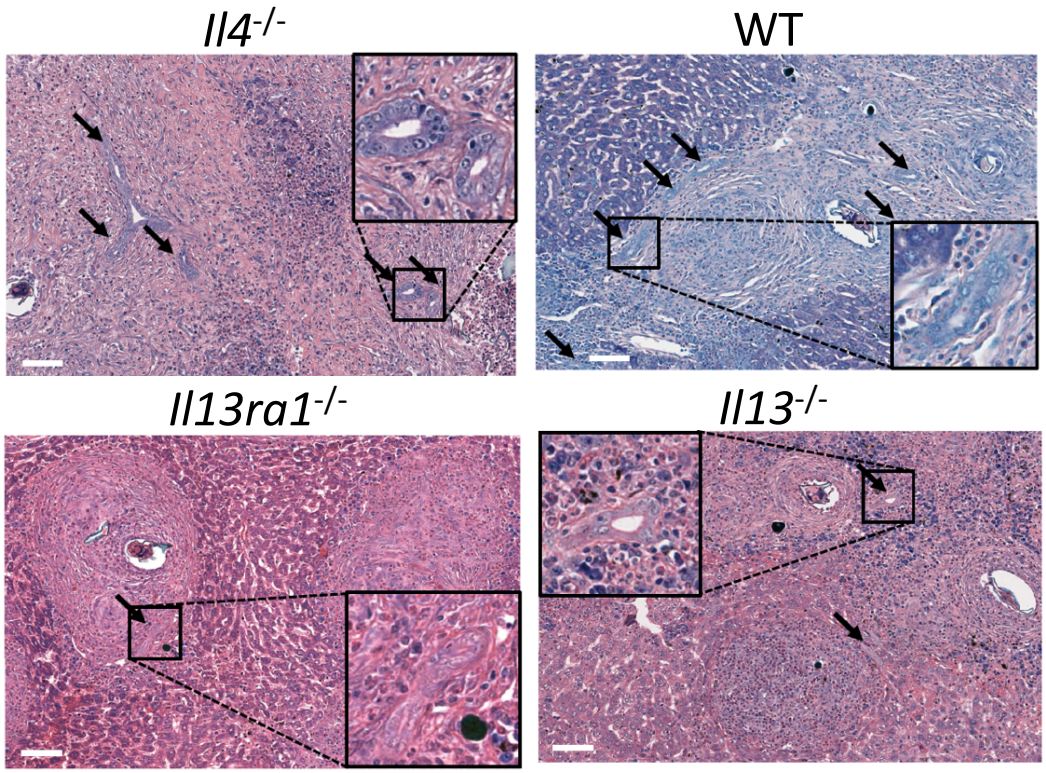


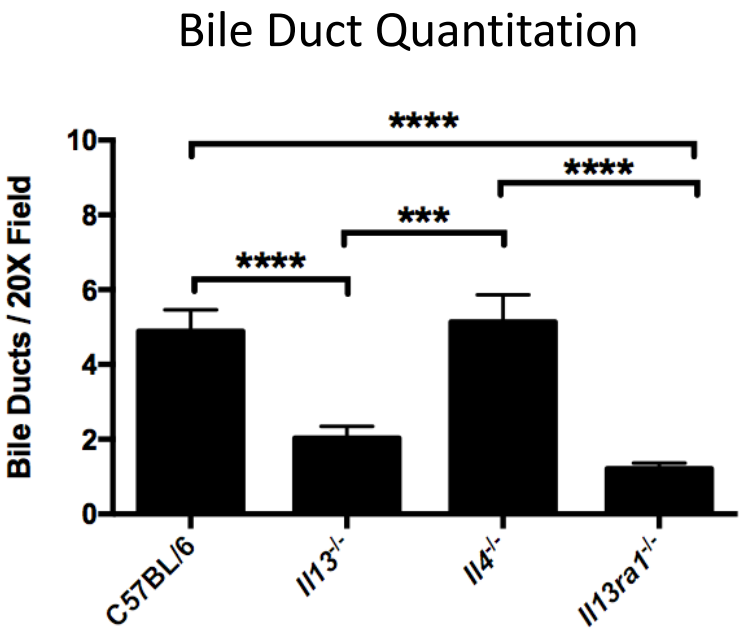
What is ductular reaction?

- Ductular reaction refers to an increased number of ductules (the finest ramifications of the biliary tree), often accompanied by inflammatory cells and an increase in matrix, leading to peri-portal fibrosis and eventually biliary cirrhosis.
- It is a phenomenon that is seen in a most chronic liver diseases.
- Patients with severe ductular reaction are at a greatest risk of requiring a transplant.
- Associated with advanced cirrhosis but whether it's a consequence of or key driver of fibrosis has remained unclear.
- Ductular reaction has also gained new interest because of its relationship with the activation of putative human liver progenitor cells.



IL-13 Signaling is Necessary for BD Proliferation

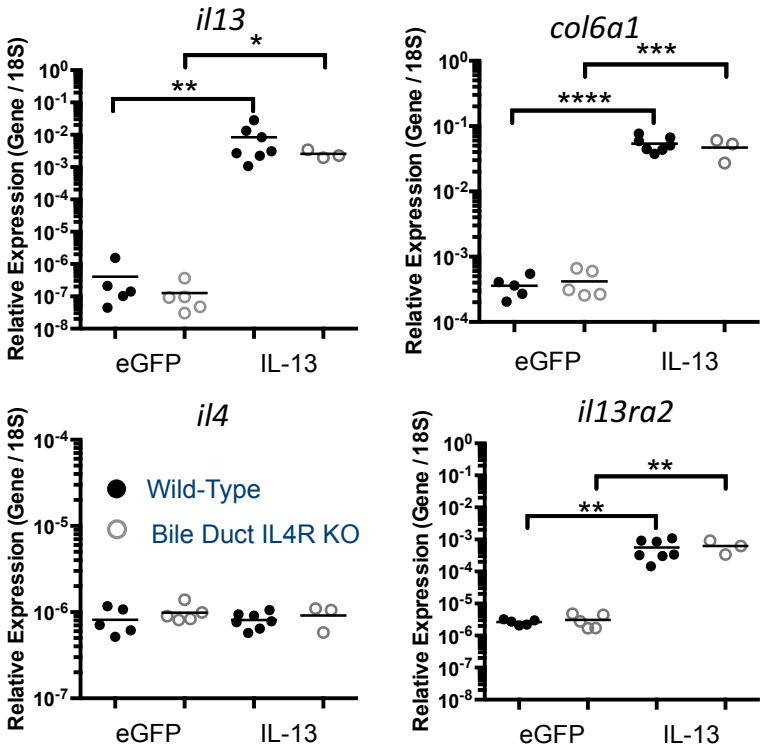




Gieseck, et al., *Immunity* 2016

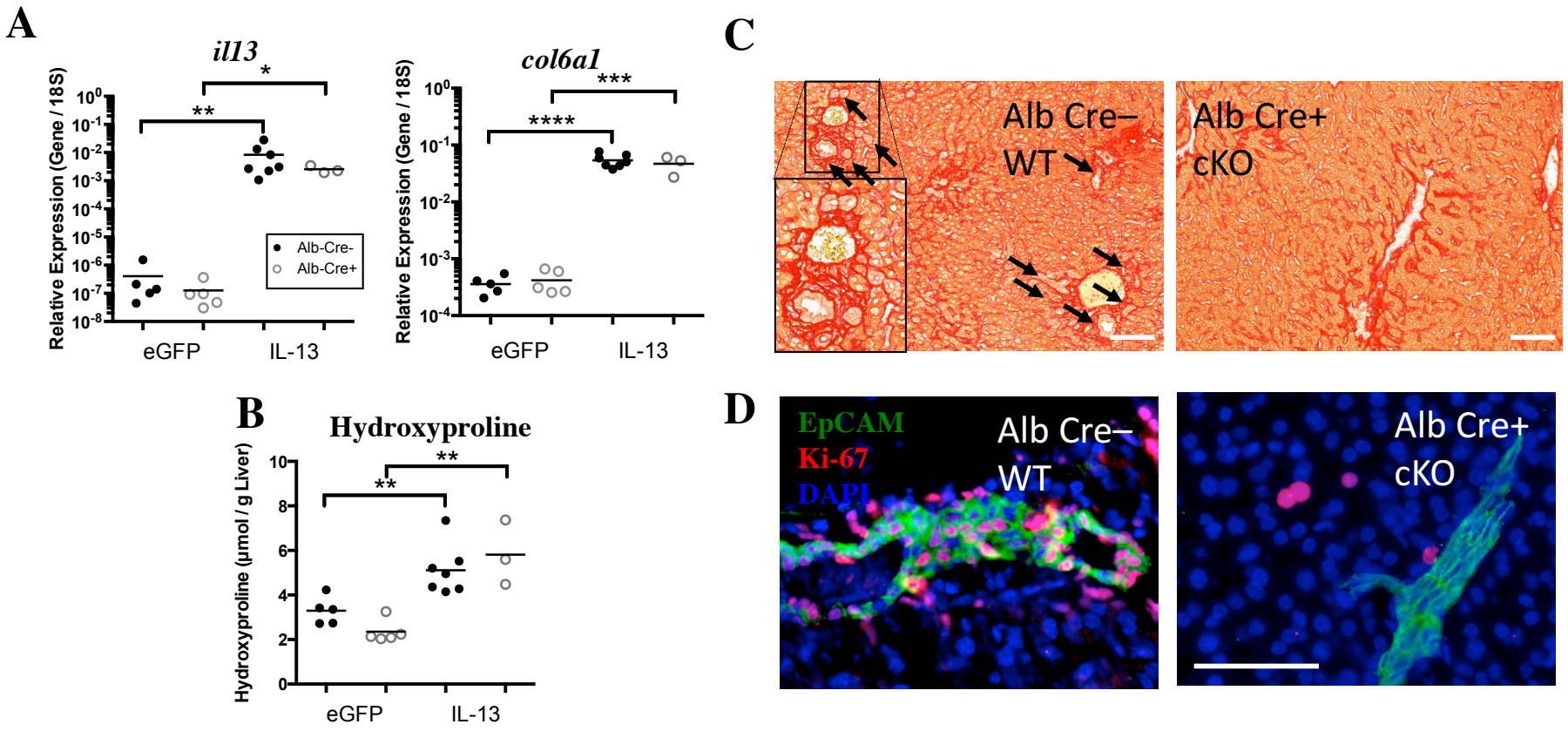
Hydrodynamic Overexpression of IL-13

IL-13 Mammalian Overexpression Plasmid



Gieseck, et al., *Immunity* 2016

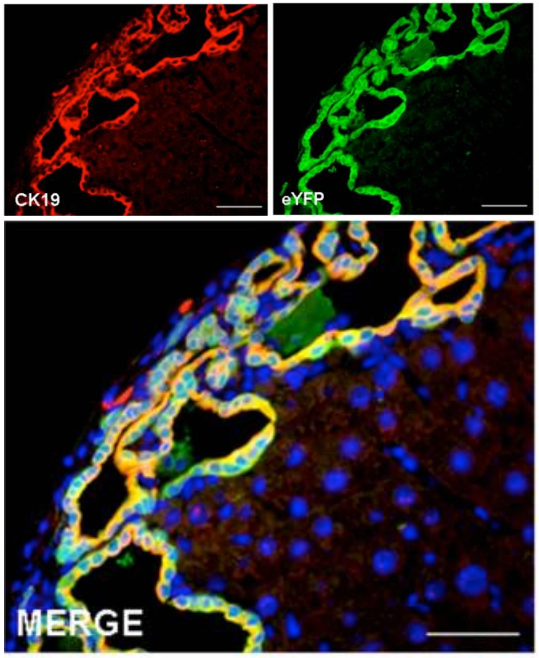
Hydrodynamic delivery of IL-13 reproduces the results obtained with *S. mansoni* infected mice



Ductular reaction (duct regeneration) is dependent on direct IL-13 signaling in hepatic/biliary cells and independent from fibrosis

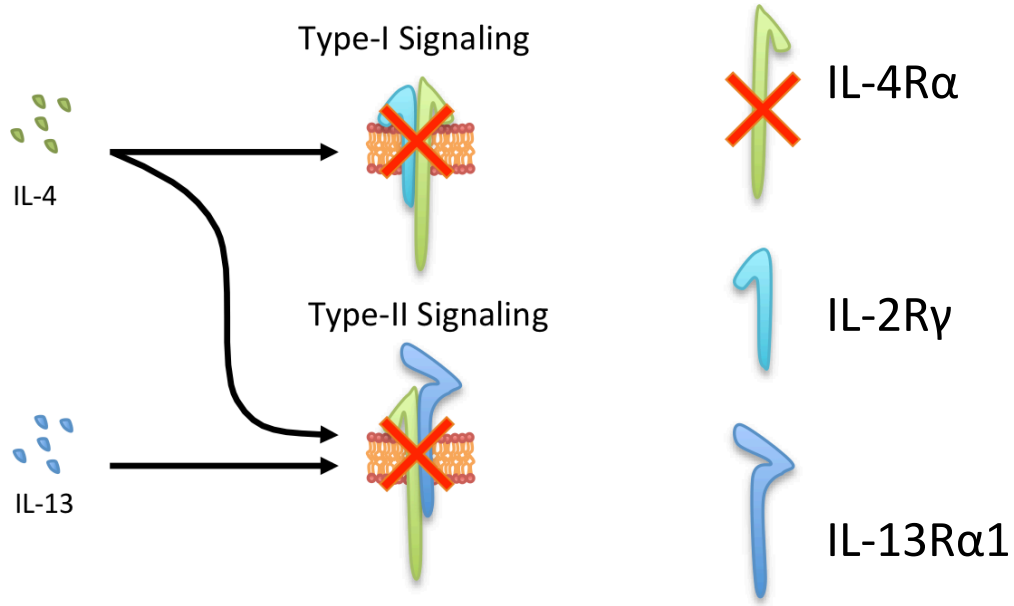
What role does the biliary compartment play in repair and fibrosis?

Krt19$^{WT/creERT}$



Guest, et al., *Cancer Res.*, 2014

Il4ra$^{Flox/Flox}$



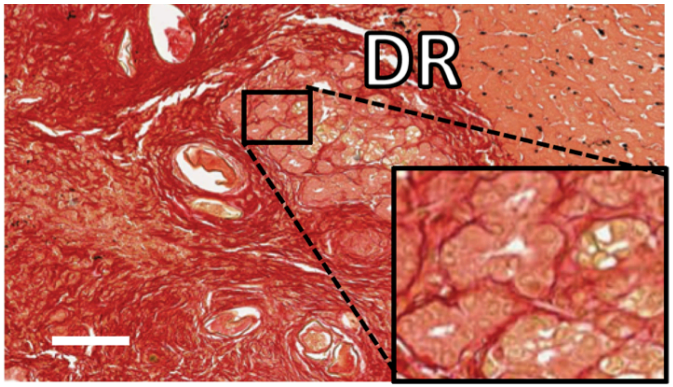
Generation of Keratin (K19)-Cre IL-4Rα $^{flox/flox}$ mice

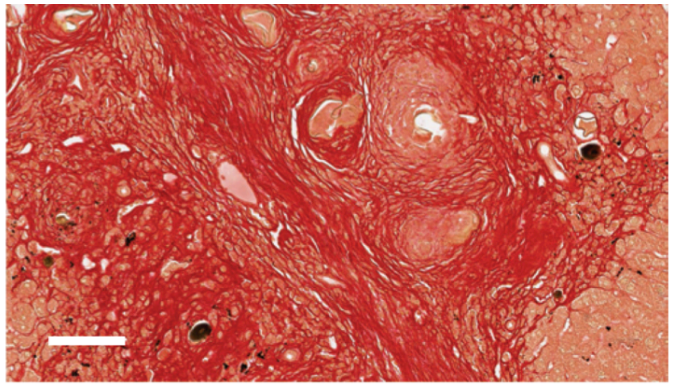
- Deficiency in IL-4/IL-13 signaling in cholangiocytes and hepatic progenitor cells but not hepatocytes

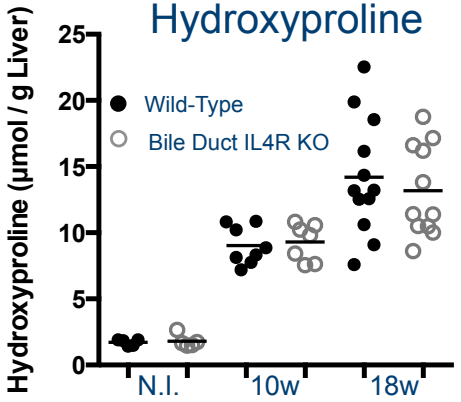
Deletion of IL-4Rα signaling specifically in the biliary compartment does not impact the development of fibrosis

Wild Type

Impaired BD
IL-13 Signaling



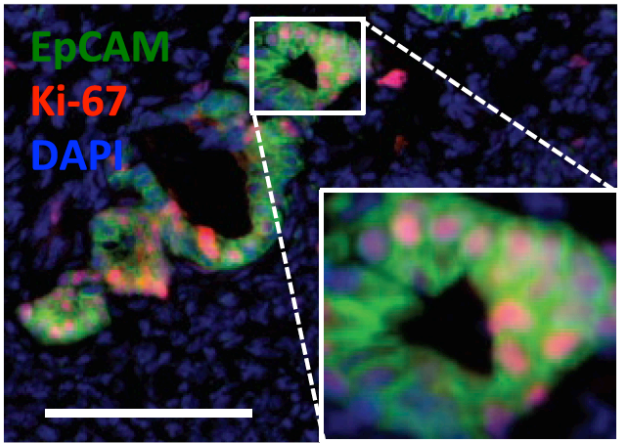




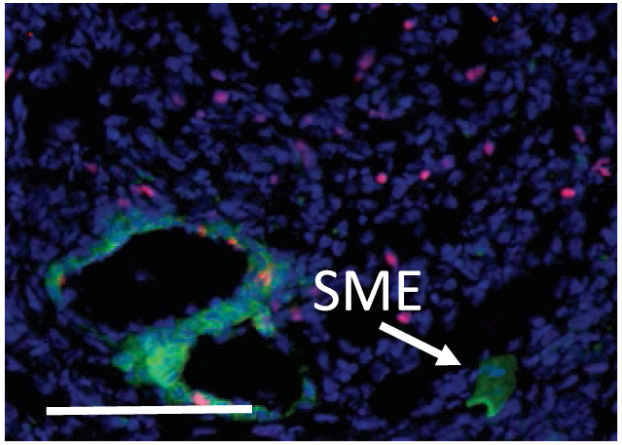
Gieseck, et al., *Immunity* 2016

IL-13 Signaling in BDs is Necessary for Ductular Reaction

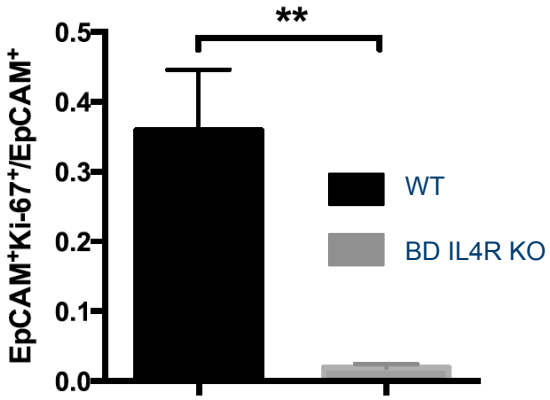
Wild Type



Impaired BD
IL-13 Signaling

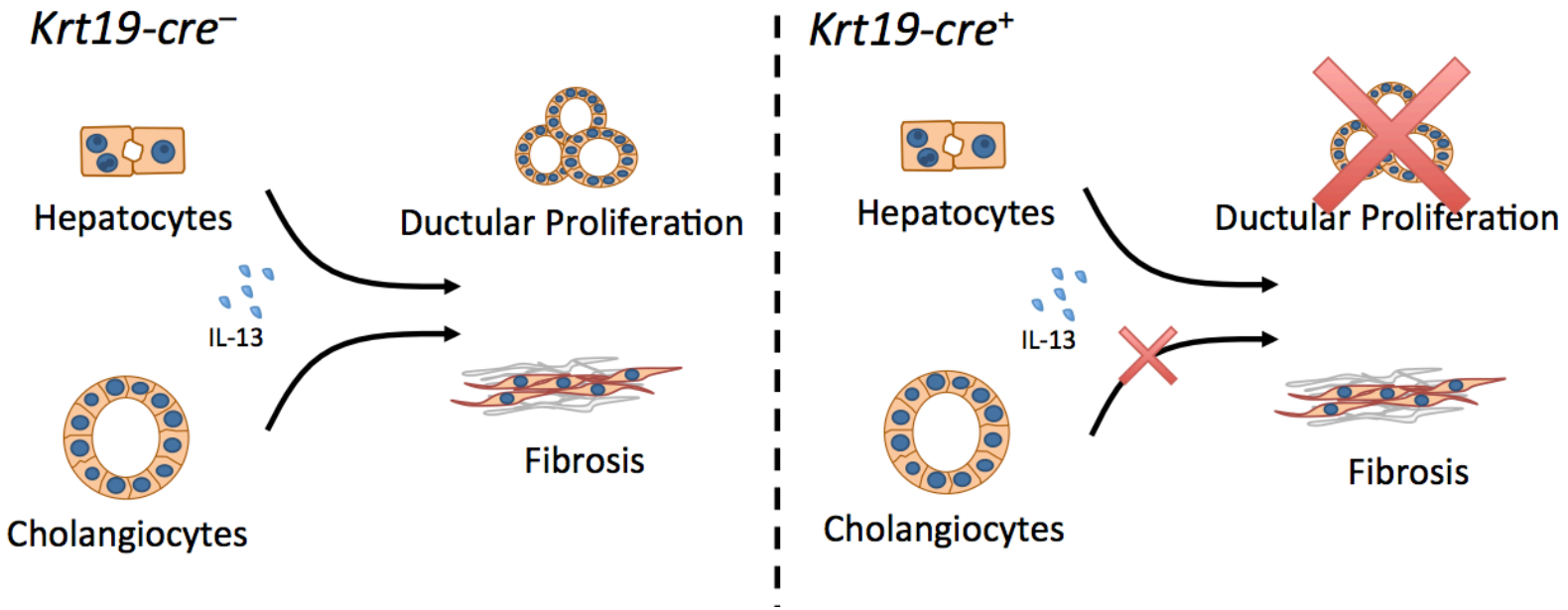


Ductular Reaction



Gieseck, et al., *Immunity* 2016

Summary: IL-13 Signaling in Bile Ducts



Gieseck, et al., *Immunity* 2016

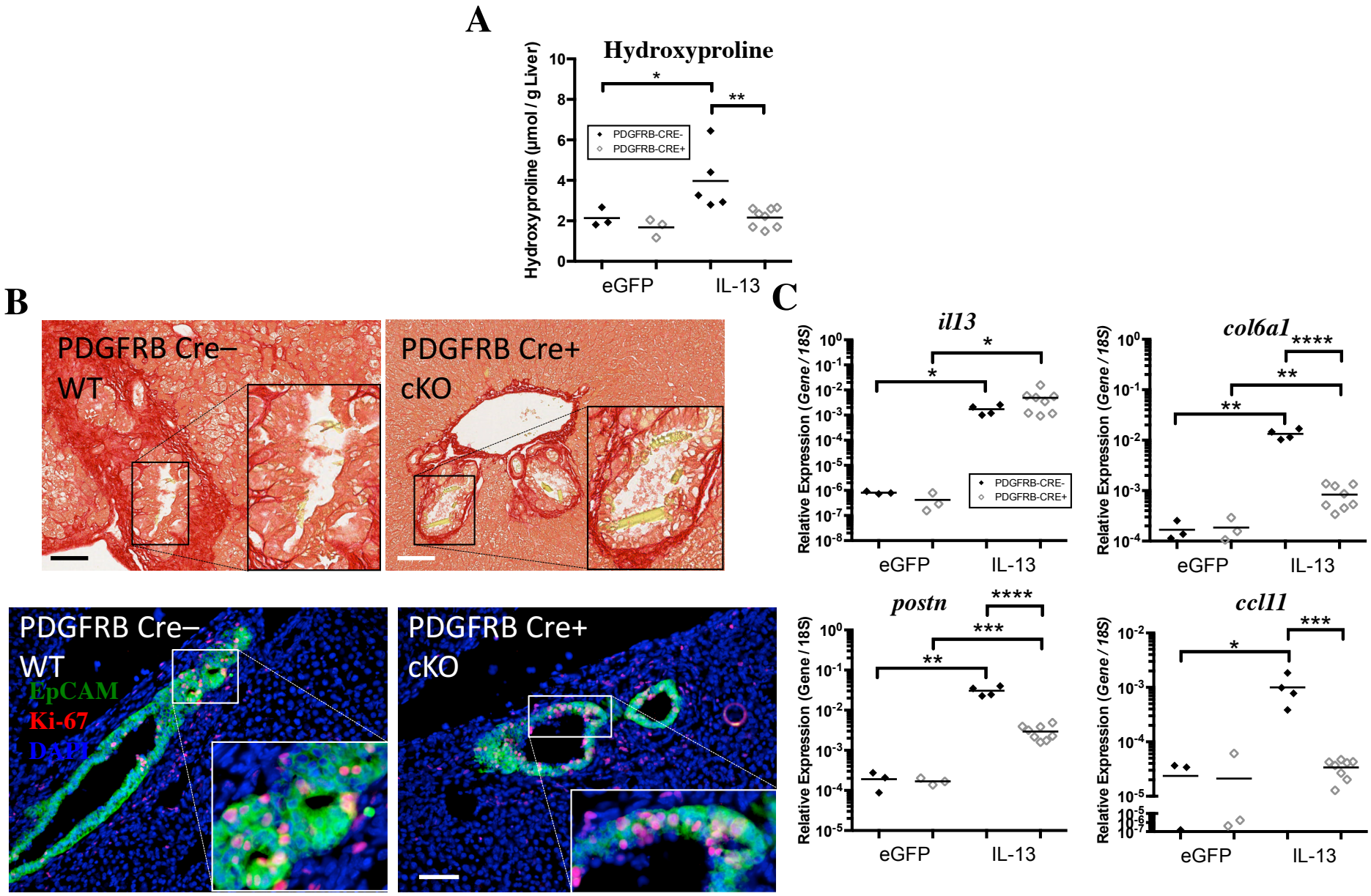
What role do fibroblasts play in IL-13 mediated repair and fibrosis?

Generation of PDGFRb-Cre IL-4Rα $^{flox/flox}$ mice

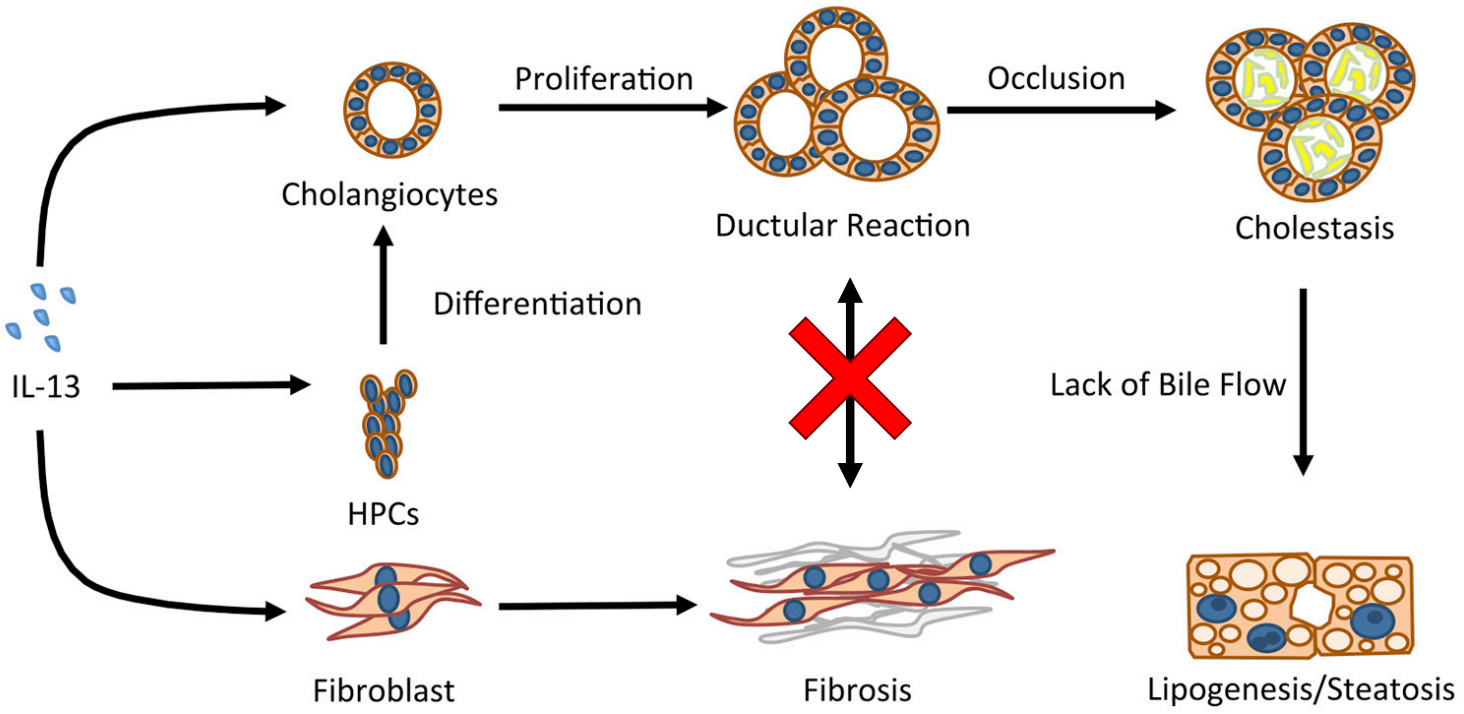
- Deficiency in IL-4/IL-13 signaling in fibroblasts

PDGFRb^{+} Fibroblasts

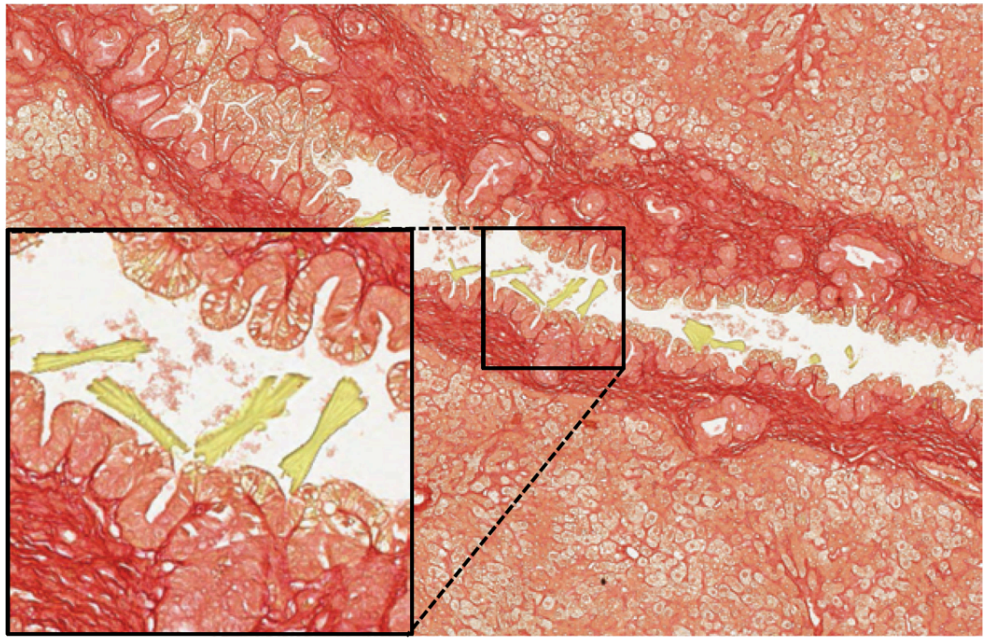
Ablation of fibrosis but not ductular expansion in PDGFRb cre mice

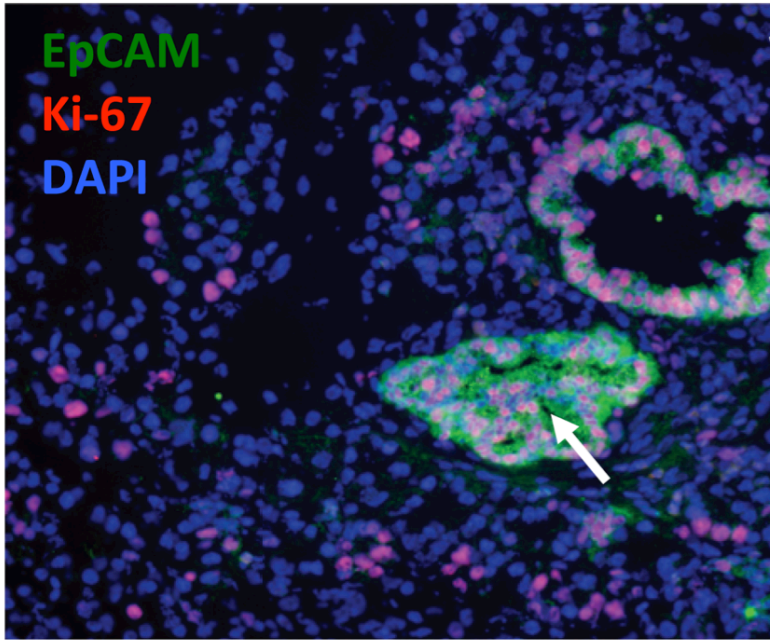


IL-13 driven ductular reaction drives cholestasis, and bile flow obstruction activates liver lipogenesis



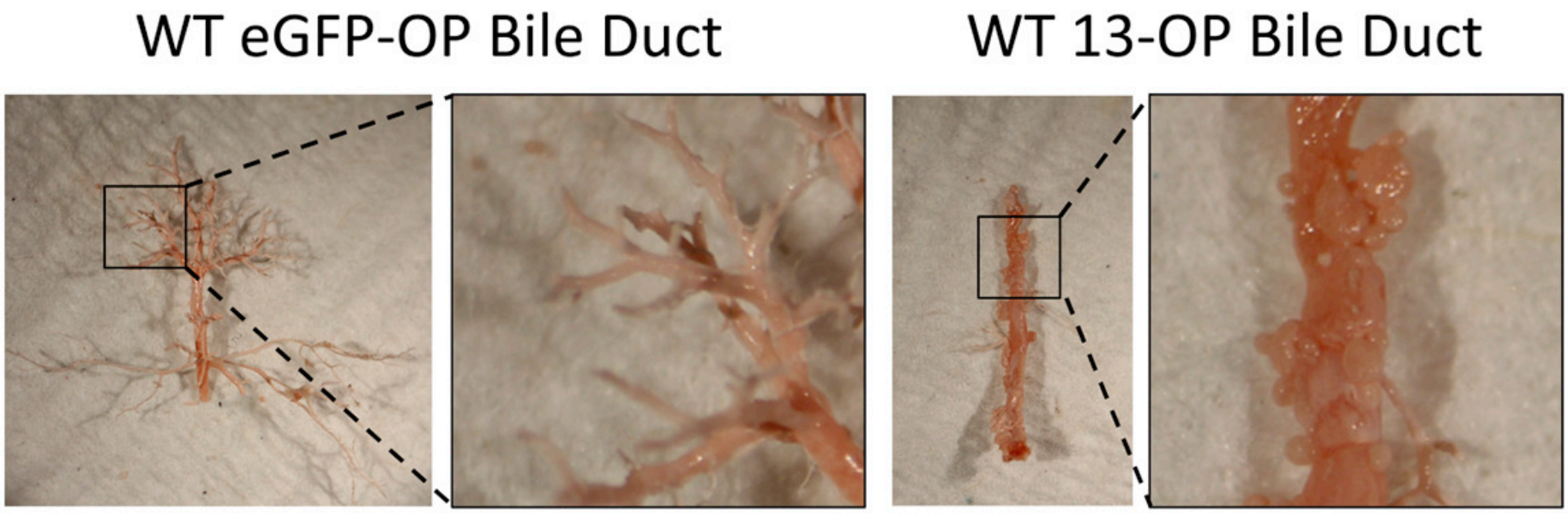
IL-13 driven ductular reaction initiates ductal cholestasis independently from fibrosis





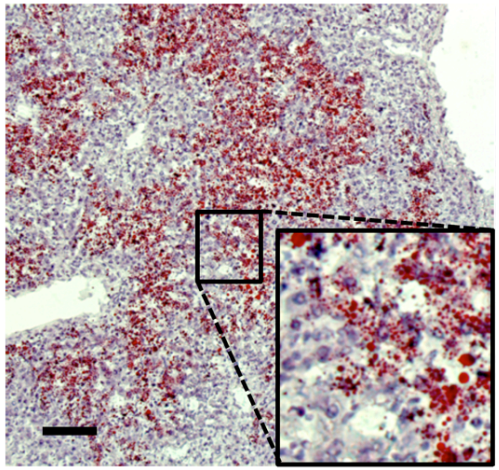
Gieseck, et al., *Immunity* 2016

IL-13 driven ductular reaction leads to bile duct obstruction and nodular regeneration

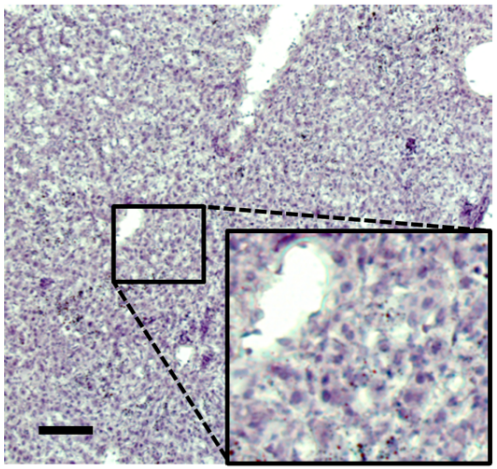


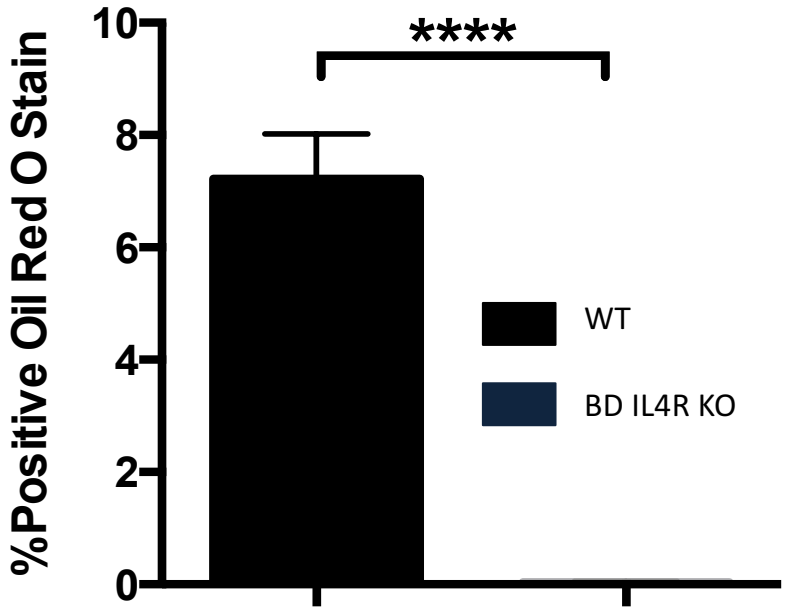
Development of fatty liver (steatosis) is dependent on IL-13 signaling in the hepatobiliary compartment

Wild Type



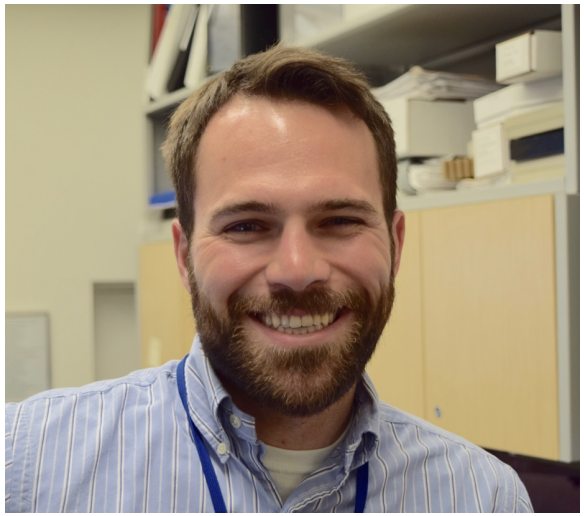
Impaired BD
IL-13 Signaling

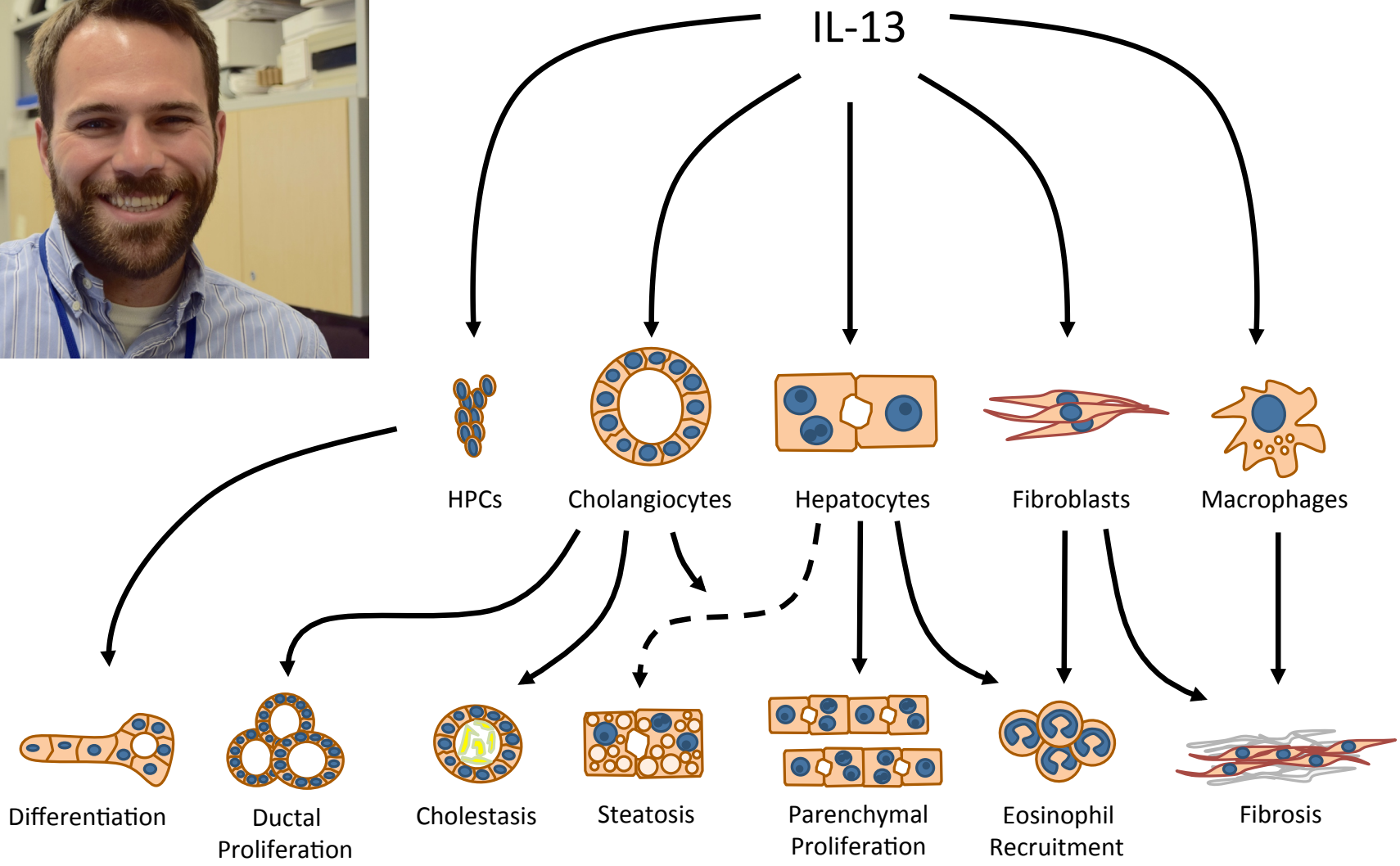




Gieseck, et al., *Immunity* 2016

Fibrosis and tissue regeneration occur simultaneously but are driven by distinct IL-13-dependent mechanisms

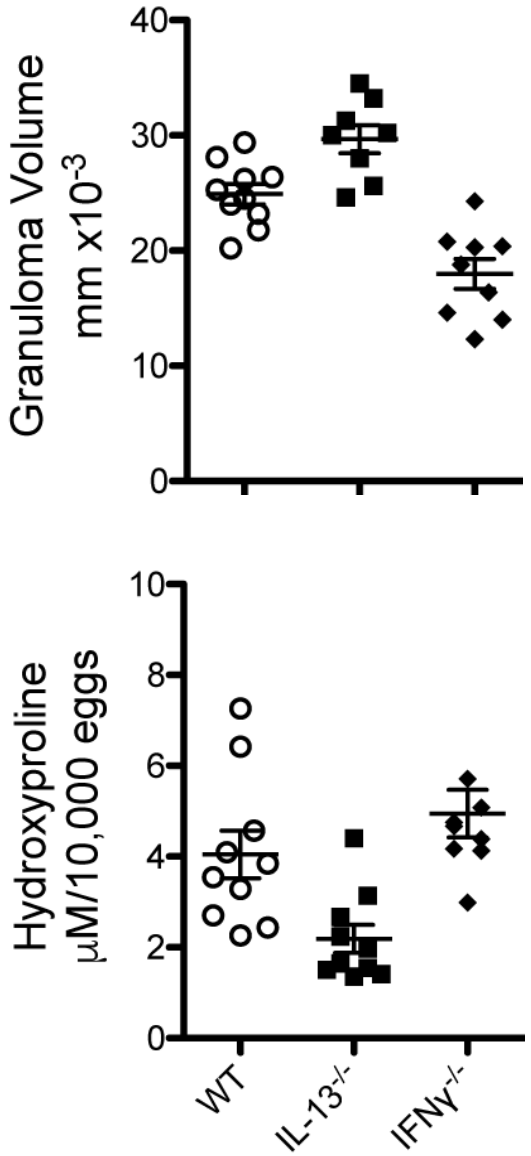




Gieseck RL (Trey). *et al*. *Immunity*. July. 2016.

Translational Potential of IL-13 blockade

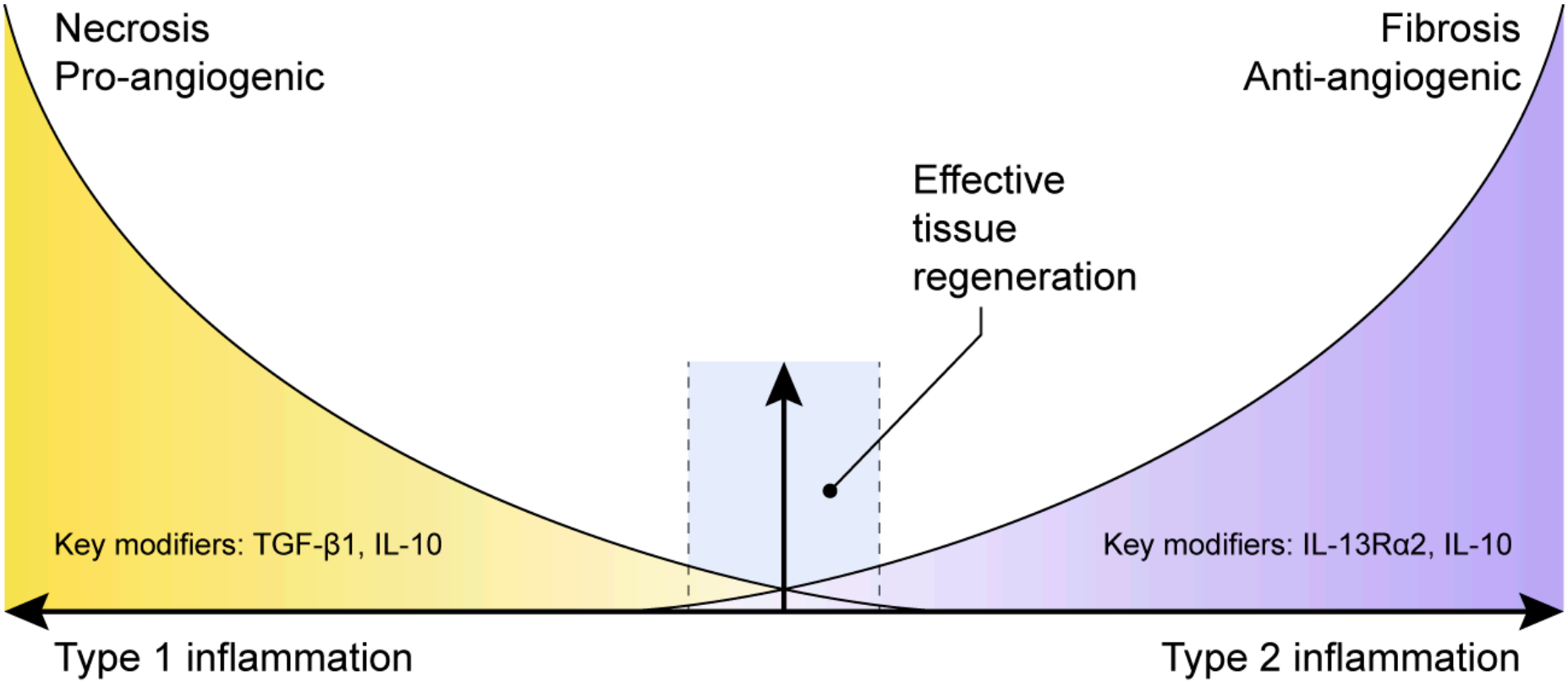
- Will rebound inflammation impair efficacy?



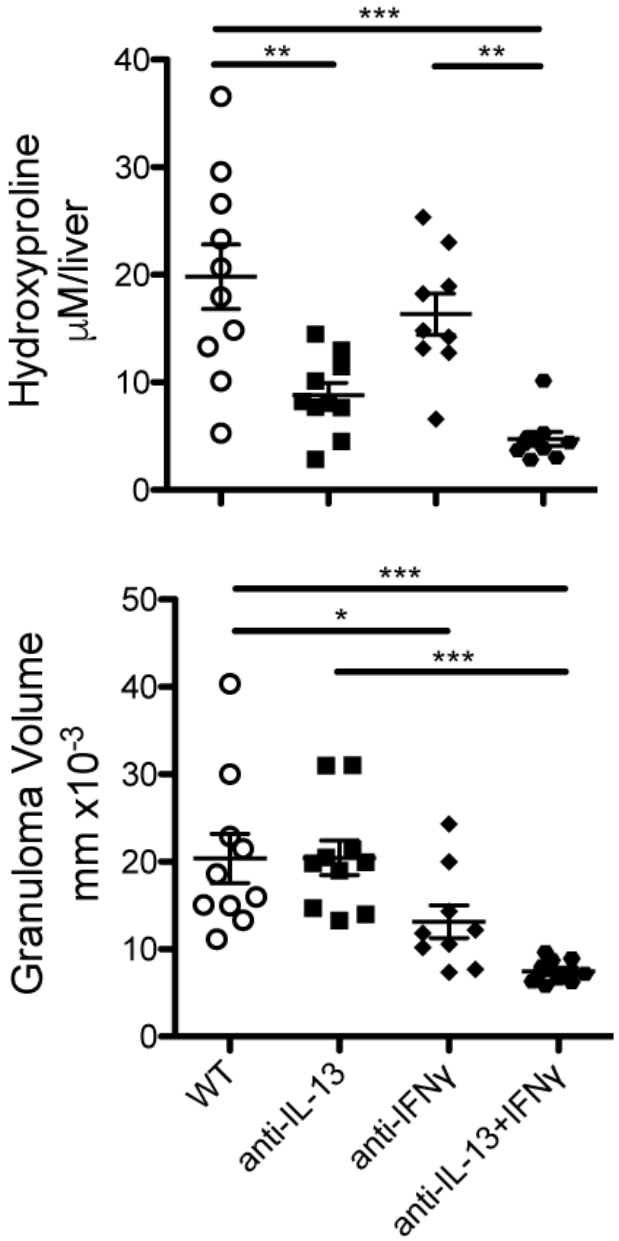
Inflammation

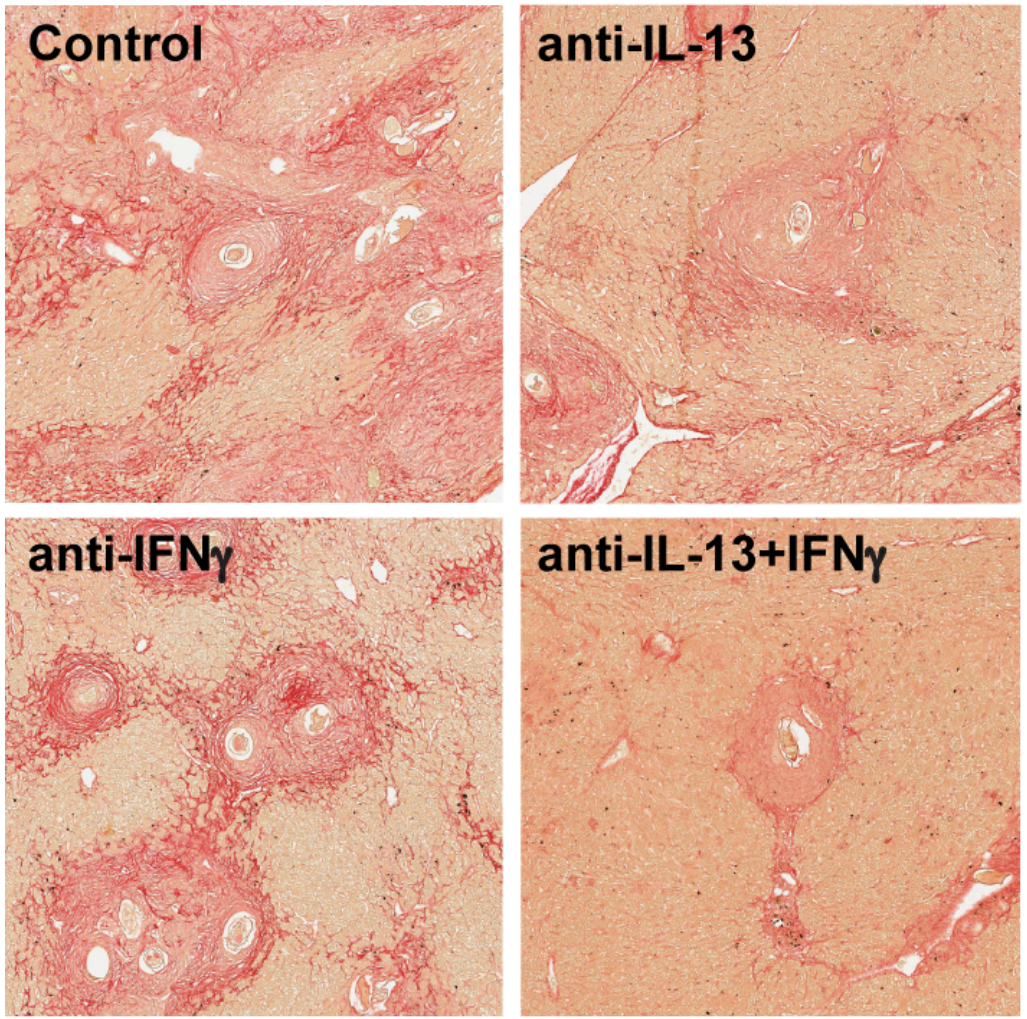
Fibrosis

An effective anti-fibrotic strategy must block the key profibrotic mediators and prevent rebound inflammation/necrosis

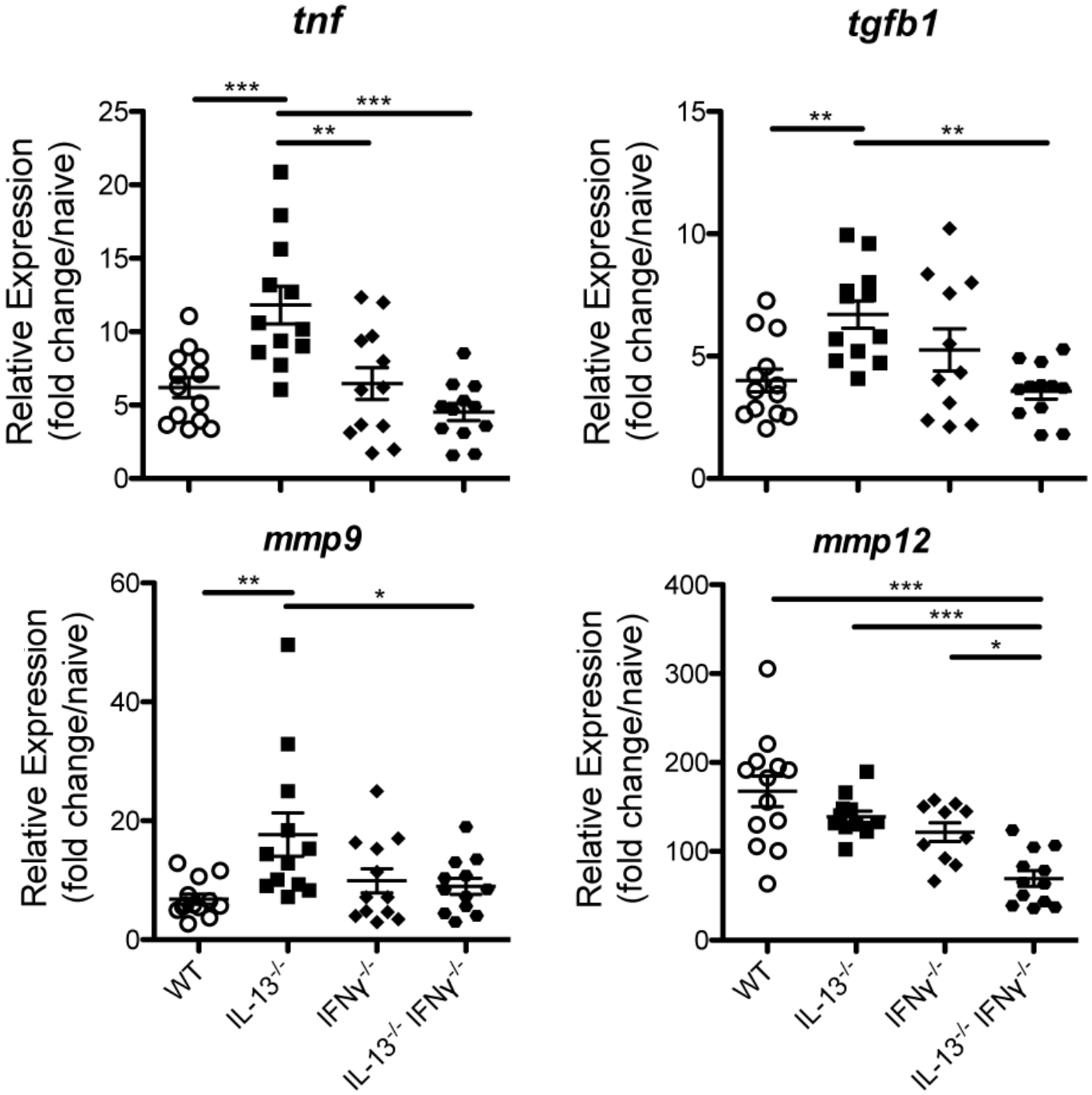


Therapeutic efficacy of antibodies to IL-13 and IFN-γ





Pro-fibrotic mediator production is maximally reduced in the combined absence of IL-13 and IFN-γ



What we know:

1. IL-13 and TGF-β are major drivers of fibrosis but they also help facilitate tissue repair and reduce inflammation.
2. Fibrosis is reversible if caught early enough.

What we don't know:

While TGF-β and IL-13 are potential therapeutic targets for fibrotic diseases, what we don't fully understand is what impact long term disruption of these pathways might have on normal tissue homeostasis and regeneration.

What we should know:

1. How to slow the progression of fibrosis without impairing normal tissue homeostasis and healing.
2. How to block fibrosis without causing damaging rebound inflammation.
3. How tissues regenerate following injury.
4. The positive and negative impact of inflammation on tissue repair and fibrosis.

Acknowledgements

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Lee Borthwick (Univ. Newcastle)
Luke Barron (UNUM Therapeutics)

Univ Cambridge
Ludovic Vallier

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Wei-Yu Lu
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